

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 21879S005**

**Name:** Nuedexta

**Sponsor:** Avanir Pharms

**Approval Date:** October 29, 2010

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA21879S005**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 21879S005**

**APPROVAL LETTER**



NDA 021879/S-005

**SUPPLEMENT APPROVAL**

Avanir Pharmaceuticals  
Attention: Arthur Rosenthal, R.A.C.  
Senior Director, Regulatory Affairs & Quality  
20 Enterprise, Suite 300  
Aliso Viejo, CA 92656

Dear Mr. Rosenthal:

Please refer to your Supplemental New Drug Application (sNDA) dated July 31, 2014, received August 1, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuedexta (dextromethorphan hydrobromide/quinidine sulfate) capsules, 20 mg/10 mg.

We acknowledge receipt of your amendment dated January 8, 2015.

This "Prior Approval" supplemental new drug application provides for clarification of the indication statement.

**APPROVAL & LABELING**

We have completed our review of this supplemental application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM H Dunn  
01/20/2015

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 21879S005**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUEDEXTA safely and effectively. See full prescribing information for NUEDEXTA.

**NUEDEXTA (dextromethorphan hydrobromide and quinidine sulfate) capsules, for oral use**  
Initial U.S. Approval: 2010

### INDICATIONS AND USAGE

NUEDEXTA is a combination product containing dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and quinidine sulfate (a CYP450 2D6 inhibitor) indicated for the treatment of pseudobulbar affect (PBA). (1)

### DOSAGE AND ADMINISTRATION

- Starting dose: one capsule daily by mouth for 7 days. (2.1)
- Maintenance dose: After 7 days, 1 capsule every 12 hours. (2.1)

### DOSAGE FORMS AND STRENGTHS

Capsules: Dextromethorphan 20 mg/Quinidine 10 mg (3)

### CONTRAINDICATIONS

- Concomitant use with quinidine, quinine, or mefloquine. (4.1)
- Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions. (4.2)
- Patients with known hypersensitivity to dextromethorphan (4.2)
- Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping NUEDEXTA before starting an MAOI. (4.3)
- Prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure (4.4)
- Complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block. (4.4)
- Concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide). (4.4)

### WARNINGS AND PRECAUTIONS

- Thrombocytopenia or other hypersensitivity reactions: Discontinue if occurs. (5.1)
- Hepatitis: Discontinue if occurs. (5.2)
- QT Prolongation: Monitor ECG if concomitant use of drugs that prolong QT interval cannot be avoided or if concomitant CYP3A4 inhibitors used. (5.3).

- Left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD): Monitor ECG in patients with LVH or LVD. (5.3)
- CYP2D6 substrate: Nuedexta inhibits CYP2D6. Accumulation of parent drug and/or failure of metabolite formation may decrease safety and/or efficacy of concomitant CYP2D6 metabolized drugs. Adjust dose of CYP2D6 substrate or use alternative treatment when clinically indicated. (5.4, 12.4)
- Dizziness: Take precautions to reduce falls. (5.5)
- Serotonin syndrome: Use of NUEDEXTA with selective serotonin reuptake inhibitor (SSRI)'s or tricyclic antidepressants increases the risk. Discontinue if occurs. (5.6, 7.4)
- Anticholinergic effects of quinidine: Monitor for worsening in myasthenia gravis and other sensitive conditions. (5.7)

### ADVERSE REACTIONS

The most common adverse reactions (incidence of  $\geq 3\%$  and two-fold greater than placebo) in patients taking NUEDEXTA are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Avanir Pharmaceuticals at (1-866-388-5041) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Desipramine: Exposure increases 8-fold. Reduce desipramine dose and adjust based on clinical response. (7.5, 12.4)
- Paroxetine: Exposure increases 2-fold. Reduce paroxetine dose and adjust based on clinical response. (7.5, 12.4)
- Digoxin: Increased digoxin substrate plasma concentration may occur. (7.6)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatric Use: Safety and effectiveness have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

01/2015

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA).

PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

The recommended starting dose of NUEDEXTA is one capsule daily by mouth for the initial seven days of therapy. On the eighth day of therapy and thereafter, the daily dose should be a total of two capsules a day, given as one capsule every 12 hours.

The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA occurs in some patients.

### 3 DOSAGE FORMS AND STRENGTHS

NUEDEXTA capsules contain 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate in a brick red gelatin capsule with “DMQ / 20-10” printed in white ink on the capsule.

### 4 CONTRAINDICATIONS

#### 4.1 Quinidine and related drugs

NUEDEXTA contains quinidine, and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine.

#### 4.2 Hypersensitivity

NUEDEXTA is contraindicated in patients with a history of NUEDEXTA, quinine, mefloquine or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome. NUEDEXTA is also contraindicated in patients with a known hypersensitivity to dextromethorphan (e.g. rash, hives) [*see Warnings and Precautions (5.1)*].

#### 4.3 MAOIs

NUEDEXTA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days, due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping NUEDEXTA before starting an MAOI [*see Drug Interactions (7.1)*].

#### 4.4 Cardiovascular

NUEDEXTA is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, and in patients with heart failure [*see Warnings and Precautions (5.3)*].

NUEDEXTA is contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide), as effects on QT interval may be increased [see *Drug Interactions (7.2)*].

NUEDEXTA is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombocytopenia and Other Hypersensitivity Reactions

Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is clearly not drug-related, as continued use increases the risk for fatal hemorrhage. Likewise, NUEDEXTA should not be restarted in sensitized patients, because more rapid and more severe thrombocytopenia than the original episode can occur. NUEDEXTA should not be used if immune-mediated thrombocytopenia from structurally related drugs, including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitizing drug.

Quinidine has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive antinuclear antibody test. Other associations include rash, bronchospasm, lymphadenopathy, hemolytic anemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevation in serum levels of skeletal-muscle enzymes, and pneumonitis.

### 5.2 Hepatotoxicity

Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. Most cases remit when quinidine is withdrawn.

### 5.3 Cardiac Effects

NUEDEXTA causes dose-dependent QTc prolongation [see *Clinical Pharmacology (12.2)*]. QT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. When initiating NUEDEXTA in patients at risk of QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3-4 hours after the first dose. This includes patients concomitantly taking/initiating drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke. LVH and LVD can be diagnosed utilizing echocardiography or another suitable cardiac imaging modality.

Strong and moderate CYP3A inhibitors include, but are not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil.

Reevaluate ECG if risk factors for arrhythmia change during the course of treatment with NUEDEXTA. Risk factors include concomitant use of drugs associated with QT prolongation, electrolyte abnormality (hypokalemia, hypomagnesemia), bradycardia, and family history of QT abnormality. Hypokalemia and

hypomagnesemia should be corrected prior to initiation of therapy with NUEDEXTA, and should be monitored during treatment.

If patients taking NUEDEXTA experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., syncope or palpitations, NUEDEXTA should be discontinued and the patient further evaluated.

#### **5.4 Concomitant use of CYP2D6 Substrates**

The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see *Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)*]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 [see *Drug Interactions (7.5)*].

#### **5.5 Dizziness**

NUEDEXTA may cause dizziness [see *Adverse Reactions (6.1)*]. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. In a controlled trial of NUEDEXTA, 10% of patients on NUEDEXTA and 5% on placebo experienced dizziness.

#### **5.6 Serotonin Syndrome**

When used with SSRIs (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine), NUEDEXTA may cause “serotonin syndrome”, with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor [see *Drug Interactions (7.4), Overdosage (10)*].

#### **5.7 Anticholinergic effects of quinidine**

Monitor for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.

#### **5.8 CYP2D6 Poor Metabolizers**

The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone [see *Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)*]. Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA.

### **6 ADVERSE REACTIONS**

A total of 946 patients participated in four Phase 3 controlled and uncontrolled PBA studies and received at least one dose of the combination product of dextromethorphan/quinidine in various strengths at the recommended or higher than the recommended dose. Of those patients, 393 patients were exposed for at least 180 days and 294 patients were exposed for at least one year. Median exposure was 168 days.

Controlled trials enrolled only patients with either ALS or MS. Uncontrolled studies enrolled 136 patients with PBA secondary to a wide variety of underlying neurological conditions including stroke (45 patients) and traumatic brain injury (23 patients). Consequently, patients with other underlying neurologic diseases may experience other adverse reactions not described below.

## 6.1 Clinical Trials Experience

A 12-week, placebo-controlled study evaluated NUEDEXTA (dextromethorphan 20 mg/quinidine 10 mg) (N=107) and a 30 mg dextromethorphan/10 mg quinidine combination (N=110) compared to placebo (N=109). Approximately 60% of patients had ALS and 40% had MS. Patients were 25 to 80 years of age, with a mean age of approximately 51 years. Three (3) ALS patients in each drug treatment arm and 1 ALS patient in the placebo arm died during the 12-week placebo-control period. All deaths were consistent with the natural progression of ALS.

### Adverse Reactions Leading to Discontinuation

The most commonly reported adverse reactions (incidence  $\geq 2\%$  and greater than placebo) that led to discontinuation with the 20 mg dextromethorphan/10 mg quinidine twice daily dose were muscle spasticity (3%), respiratory failure (1%), abdominal pain (2%), asthenia (2%), dizziness (2%), fall (1%), and muscle spasms (2%).

### Most Common Adverse Reactions

Adverse drug reactions that occurred in  $\geq 3\%$  of patients receiving the 20 mg dextromethorphan/10 mg quinidine twice daily dose, and at an incidence of  $\geq 2$  times placebo in short-term clinical trials in ALS and MS are provided in Table 1. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Table 1: Adverse Drug Reactions with an Incidence of  $\geq 3\%$  of Patients and  $\geq 2$ x Placebo in NUEDEXTA-treated Patients by System-Organ Class and Preferred Term**

	NUEDEXTA N=107	Placebo N=109
	%	%
Diarrhea	13	6
Dizziness	10	5
Cough	5	2
Vomiting	5	1
Asthenia	5	2
Peripheral edema	5	1
Urinary tract infection	4	1
Influenza	4	1
Increased gamma-glutamyltransferase	3	0
Flatulence	3	1

## 6.2 Long-Term Exposure with NUEDEXTA

The experience in open-label clinical trials is consistent with the safety profile observed in the placebo-controlled clinical trials

## 6.3 Safety Experience of Individual Components

The following adverse reactions have been reported with the use of the individual components of NUEDEXTA, dextromethorphan and quinidine, from post-marketing experience. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Dextromethorphan

Drowsiness, dizziness, nervousness or restlessness, nausea, vomiting, and stomach pain.

### Quinidine

Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose of several hundred milligrams. Cinchonism is characterized by nausea, vomiting, diarrhea, headache tinnitus, hearing loss, vertigo, blurred vision, diplopia, photophobia, confusion, and delirium.

Convulsions, apprehension, and ataxia have been reported with quinidine therapy, but it is not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion in patients being treated for cardiovascular indications. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare. Other adverse reactions occasionally reported with quinidine therapy include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, keratopathy, and abnormalities of skin pigmentation.

## **7 DRUG INTERACTIONS**

### **7.1 MAOIs**

Do not use NUEDEXTA with monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days [*see Contraindications (4.3)*].

### **7.2 Drugs that Prolong QT and are Metabolized by CYP2D6**

Do not use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide) [*see Contraindications (4.4)*].

### **7.3 Drugs that Prolong QT and Concomitant CYP3A4 Inhibitors**

Recommend ECG in patients taking drugs with NUEDEXTA that prolong the QT interval and in patients taking concomitant moderate or strong CYP3A4 inhibitors [*see Warnings and Precautions (5.3)*].

### **7.4 SSRIs and Tricyclic Antidepressants**

Use of NUEDEXTA with SSRIs or tricyclic antidepressants increases the risk of ‘serotonin syndrome’ [*see Warnings and Precautions (5.6)*].

### **7.5 CYP2D6 Substrate**

The co-administration of NUEDEXTA with drugs that undergo extensive CYP2D6 metabolism may result in altered drug effects, due to accumulation of parent drug and/or failure of metabolite formation [*see Warnings and Precautions (5.4)*]. Therapy with medications that are primarily metabolized by CYP2D6 and that have a relatively narrow therapeutic index should be initiated at a low dose if a patient is receiving NUEDEXTA concurrently. If NUEDEXTA is added to the treatment regimen of a patient already receiving a drug primarily metabolized by CYP2D6, the need for a dose modification of the original medication should be considered. The extent to which CYP2D6 interactions may pose clinical problems will depend on the pharmacokinetics of the substrate involved.

In cases of prodrugs whose actions are mediated by the CYP2D6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in the presence of NUEDEXTA due to quinidine-mediated inhibition of CYP2D6. Consider use of alternative treatment with NUEDEXTA when clinically indicated.

Drug interactions with desipramine and paroxetine have been studied in controlled clinical trials with a higher dose combination of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) than NUEDEXTA; study results are described below. No other drug interactions with CYP2D6 substrates have been systematically investigated, although concomitant use of such drugs was allowed in clinical trials with NUEDEXTA and in clinical trials with higher dose formulations of dextromethorphan/quinidine.

Desipramine (CYP2D6 substrate):

The tricyclic antidepressant desipramine is metabolized primarily by CYP2D6. A drug interaction study was conducted between a higher combination dose of dextromethorphan (dextromethorphan 30 mg/quinidine 30 mg) and desipramine 25 mg. The combination dose of dextromethorphan/quinidine increased steady state desipramine levels approximately 8-fold. If NUEDEXTA and desipramine are prescribed concomitantly, the initial dose of desipramine should be markedly reduced. The dose of desipramine can then be adjusted based on clinical response; however, a dose above 40 mg/day is not recommended.

Paroxetine (CYP2D6 inhibitor and substrate):

When the combination dose of dextromethorphan 30 mg/quinidine 30 mg was added to paroxetine at steady state, paroxetine exposure ( $AUC_{0-24}$ ) increased by 1.7 fold and  $C_{max}$  increased by 1.5 fold. Consideration should be given to initiating treatment with a lower dose of paroxetine if given with NUEDEXTA. The dose of paroxetine can then be adjusted based on clinical response; however, dosage above 35 mg/day is not recommended.

## **7.6 Digoxin**

Quinidine is an inhibitor of P-glycoprotein. Concomitant administration of quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. Plasma digoxin concentrations should be closely monitored in patients taking NUEDEXTA concomitantly, and the digoxin dose reduced, as necessary.

## **7.7 Alcohol**

As with any other CNS drug, caution should be used when NUEDEXTA is taken in combination with other centrally acting drugs and alcohol.

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

Pregnancy Category C:

There are no adequate and well-controlled studies of NUEDEXTA in pregnant women. In oral studies conducted in rats and rabbits, a combination of dextromethorphan/quinidine demonstrated developmental toxicity, including teratogenicity (rabbits) and embryolethality, when given to pregnant animals. NUEDEXTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

When dextromethorphan/quinidine was administered orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-fetal deaths were observed at the highest dose tested and reduced skeletal ossification was observed at all doses. The lowest dose tested (5/100 mg/kg/day) is approximately 1/50 times the recommended human dose (RHD) of 40/20 mg/day on a mg/m<sup>2</sup> basis. Oral administration (0/0, 5/60, 15/60, and 30/60 mg/kg/day) to pregnant rabbits during

organogenesis resulted in an increased incidence of fetal malformations at all but the lowest dose tested. The no-effect dose (5/60 mg/kg/day) is approximately 2/60 times the RHD on a mg/m<sup>2</sup> basis.

When dextromethorphan/quinidine was orally administered (0/0, 5/100, 15/100, and 30/100 mg/kg/day) to female rats during pregnancy and lactation, pup survival and pup weight were decreased at all doses and developmental delay was seen in offspring at the mid- and high-doses. The lowest dose tested (5/100 mg/kg/day) is approximately 1/50 times the RHD on a mg/m<sup>2</sup> basis.

## **8.2 Labor and Delivery**

The effects of NUEDEXTA on labor and delivery are unknown.

## **8.3 Nursing Mothers**

It is not known whether dextromethorphan or quinidine are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NUEDEXTA is administered to a nursing mother.

## **8.4 Pediatric Use**

The safety and effectiveness of NUEDEXTA in pediatric patients below the age of 18 have not been established.

## **8.5 Geriatric Use**

Of the total number of patients with PBA in clinical studies of NUEDEXTA, 14 percent were 65 years old and over, while 2 percent were 75 and over. Clinical study of NUEDEXTA did not include sufficient number of patients aged 65 and over to determine whether they respond differently than younger patients.

## **8.6 Renal Impairment**

Dose adjustment of NUEDEXTA is not required in patients with mild to moderate renal impairment [*see Clinical Pharmacology (12.3)*]. The pharmacokinetics of NUEDEXTA have not been evaluated in patients with severe renal impairment; however, increases in dextromethorphan and/or quinidine levels are likely to be observed.

## **8.7 Hepatic Impairment**

Dose adjustment of NUEDEXTA is not required in patients with mild to moderate hepatic impairment. The pharmacokinetics of NUEDEXTA have not been evaluated in patients with severe hepatic impairment; however, increases in dextromethorphan and/or quinidine levels are likely to be observed.

## **9 DRUG ABUSE AND DEPENDENCE**

NUEDEXTA is a low-affinity uncompetitive NMDA antagonist and sigma-1 receptor agonist that has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, NUEDEXTA is a combination product containing dextromethorphan and quinidine, and cases of dextromethorphan abuse have been reported, predominantly in adolescents.

While clinical trials did not reveal drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which NUEDEXTA will be misused, diverted, and/or abused once marketed. Therefore, patients with a history of drug abuse should be observed closely for signs of NUEDEXTA misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behavior).

## **10 OVERDOSAGE**

Evaluation and treatment of NUEDEXTA overdose is based on experience with the individual components, dextromethorphan and quinidine. Metabolism of the dextromethorphan component of NUEDEXTA is inhibited by the quinidine component, such that adverse effects of overdose due to NUEDEXTA might be more severe or more persistent compared to overdose of dextromethorphan alone.

During development of NUEDEXTA, dose combinations of dextromethorphan/quinidine containing up to 6-times higher dextromethorphan dose and 12-times higher quinidine dose were studied. The most common adverse events were mild to moderate nausea, dizziness, and headache.

The most important adverse effects of acute quinidine overdose are ventricular arrhythmias and hypotension. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium.

While therapeutic doses of quinidine for treatment of cardiac arrhythmia or malaria are generally 10-fold or more higher than the dose of quinidine in NUEDEXTA, potentially fatal cardiac arrhythmia, including torsades de pointes, can occur at quinidine exposures that are possible from NUEDEXTA overdose.

Adverse effects of dextromethorphan overdose include nausea, vomiting, stupor, coma, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse effects include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes. Dextromethorphan may cause serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents, SSRIs or tricyclic antidepressants.

### **10.1 Treatment of Overdose**

While serum quinidine levels can be measured, electrocardiographic monitoring of the QTc interval is a better predictor of quinidine-induced arrhythmia. Treatment of hemodynamically unstable polymorphic ventricular tachycardia (including torsades de pointes) is either immediate cardioversion or, if a cardiac pacemaker is in place or immediately available, immediate overdrive pacing. After pacing or cardioversion, further management must be guided by the length of the QTc interval. Factors contributing to QTc prolongation (especially hypokalemia and hypomagnesemia) should be sought out and (if possible) aggressively corrected. Prevention of recurrent torsades de pointes may require sustained overdrive pacing or the cautious administration of isoproterenol (30-150 ng/kg/min).

Because of the theoretical possibility of QT-prolonging effects that might be additive to those of quinidine, other antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided.

If the post-cardioversion QTc interval is prolonged, then the pre-cardioversion polymorphic ventricular tachyarrhythmia was (by definition) torsades de pointes. In this case, class Ib antiarrhythmics like lidocaine are unlikely to be of value, and other Class I and Class III antiarrhythmics are likely to exacerbate the situation.

Quinidine-induced hypotension that is not due to an arrhythmia is likely to be a consequence of quinidine-related  $\alpha$ -blockade and vasorelaxation. Treatment of hypotension should be directed at symptomatic and supportive measures. Repletion of central volume (Trendelenburg positioning, saline infusion) may be sufficient therapy; other interventions reported to have been beneficial in this setting are those that increase peripheral vascular resistance, including  $\alpha$ -agonist catecholamines (norepinephrine).

Quinidine:

Adequate studies of orally administered activated charcoal in human overdoses of quinidine have not been reported, but there are animal data showing significant enhancement of systemic elimination following this intervention, and there is at least one human case report in which the elimination half-life of quinidine in the serum was apparently shortened by repeated gastric lavage. Activated charcoal should be avoided if an ileus is present; the conventional dose is 1 gram/kg, administered every 2 to 6 hours as a slurry with 8 mL/kg of tap water. Although renal elimination of quinidine might theoretically be accelerated by maneuvers to acidify the urine, such maneuvers are potentially hazardous and of no demonstrated benefit. Quinidine is not usefully removed from the circulation by dialysis. Following quinidine overdose, drugs that delay elimination of quinidine (cimetidine, carbonic anhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

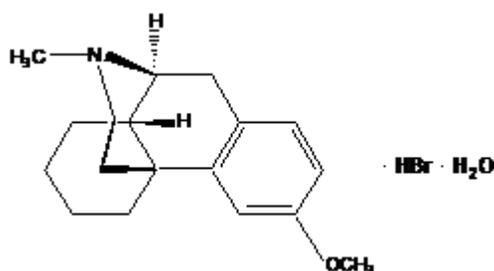
#### Dextromethorphan:

Treatment of dextromethorphan overdosage should be directed at symptomatic and supportive measures.

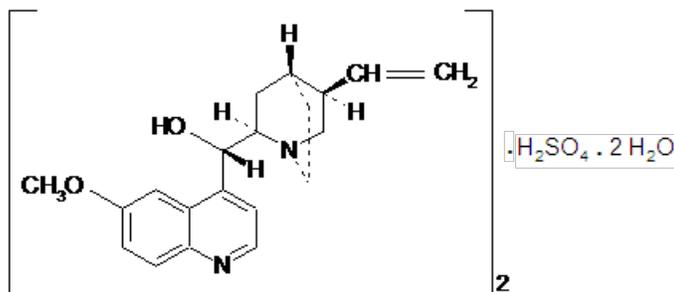
### 11 DESCRIPTION

NUEDEXTA is an oral formulation of dextromethorphan hydrobromide USP and quinidine sulfate USP in a fixed dose combination.

Dextromethorphan hydrobromide is the pharmacologically active ingredient of NUEDEXTA that acts on the central nervous system (CNS). The chemical name is dextromethorphan hydrobromide: morphinan, 3-methoxy-17-methyl-, (9 $\alpha$ , 13 $\alpha$ , 14 $\alpha$ ), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula  $C_{18}H_{25}NO \cdot HBr \cdot H_2O$  with a molecular weight of 370.33. The structural formula is:



Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in NUEDEXTA to increase the systemic bioavailability of dextromethorphan. The chemical name is quinidine sulfate: cinchonan-9-ol, 6'-methoxy-, (9S) sulfate (2:1), (salt), dihydrate. Quinidine sulfate dihydrate has the empirical formula of  $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$  with a molecular weight of 782.96. The structural formula is:



The combination product, NUEDEXTA, is a white to off-white powder. NUEDEXTA is available for oral use as NUEDEXTA which contains 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate. The active ingredients are dextromethorphan hydrobromide monohydrate USP and quinidine

sulfate dihydrate USP. Inactive ingredients in the capsule are croscarmellose sodium NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, lactose monohydrate NF, and magnesium stearate NF.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Dextromethorphan (DM) is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist. Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. The mechanism by which dextromethorphan exerts therapeutic effects in patients with pseudobulbar affect is unknown.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

The effects of suprathreshold doses of dextromethorphan/quinidine (30 mg/30mg and 60mg/60mg, for 7 doses) on QTc prolongation was evaluated in a randomized, placebo-controlled, double-blind, crossover design with an additional open-label positive control (400-mg moxifloxacin) arm in 36 healthy volunteers. The maximum mean (95% upper confidence bound) differences from placebo after baseline-correction were 10.2 (14.6) and 18.4 (22.7) ms following dextromethorphan/quinidine doses of 30 mg/30 mg and 60/60 mg, respectively. The suprathreshold doses are adequate to represent exposure increases due to drug-drug interactions and organ dysfunctions.

### 12.3 Pharmacokinetics

NUEDEXTA contains dextromethorphan and quinidine, both of which are metabolized primarily by liver enzymes. Quinidine's primary pharmacological action in NUEDEXTA is to competitively inhibit the metabolism of dextromethorphan catalyzed by CYP2D6 in order to increase and prolong plasma concentrations of dextromethorphan [see *Warnings and Precautions (5.4), (5.8), and Clinical Pharmacology (12.5)*]. Studies were conducted with the individual components of NUEDEXTA in healthy subjects to determine single-dose and multiple-dose kinetics of orally administered dextromethorphan in combination with quinidine. The increase in dextromethorphan levels appeared approximately dose proportional when the dextromethorphan dose was increased from 20 mg to 30 mg in the presence of 10 mg of quinidine.

#### Absorption

Following single and repeated combination doses of dextromethorphan 30 mg/quinidine 10 mg, dextromethorphan/quinidine -treated subjects had an approximately 20-fold increase in dextromethorphan exposure compared to dextromethorphan given without quinidine.

Following repeated doses of dextromethorphan 30 mg/quinidine 10 mg and dextromethorphan 20 mg/quinidine 10 mg (NUEDEXTA), maximal plasma concentrations ( $C_{max}$ ) of dextromethorphan are reached approximately 3 to 4 hours after dosing and maximal plasma concentrations of quinidine are reached approximately 1 to 2 hours after dosing.

In extensive metabolizers, mean  $C_{\max}$  and  $AUC_{0-12}$  values of dextromethorphan and dextrophan increased as doses of dextromethorphan increased from 20 to 30 mg; mean  $C_{\max}$  and  $AUC_{0-12}$  values of quinidine appeared similar.

The mean plasma  $C_{\max}$  of quinidine following twice daily co-administration of dextromethorphan 30 mg/quinidine 10 mg in patients with PBA was within 1 to 3% of the concentrations required for antiarrhythmic efficacy (2 to 5 mcg/mL).

NUEDEXTA may be taken without regard to meals as food does not affect the exposure of dextromethorphan and quinidine significantly.

### Distribution

After NUEDEXTA administration, protein binding remains essentially the same as that after administration of the individual components; dextromethorphan is approximately 60-70% protein bound and quinidine is approximately 80-89% protein bound.

### Metabolism and Excretion

NUEDEXTA is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 30mg/quinidine 30mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours.

There are several hydroxylated metabolites of quinidine. The major metabolite of quinidine is 3-hydroxyquinidine. The 3-hydroxymetabolite is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects such as QT prolongation.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption.

### Specific Populations

#### *Geriatric Use*

The pharmacokinetics of dextromethorphan/quinidine have not been investigated systematically in elderly subjects (aged >65 years), although such subjects were included in the clinical program. A population pharmacokinetic analysis of 170 subjects (148 subjects < 65 years old and 22 subjects ≥ 65 years old) administered dextromethorphan 30 mg/quinidine 30 mg revealed similar pharmacokinetics in subjects <65 years and those ≥ 65 years of age.

#### *Pediatric Use*

The pharmacokinetics of NUEDEXTA in pediatric patients have not been studied.

#### *Gender*

A population pharmacokinetic analysis based on data from 109 subjects (75 male; 34 female) showed no apparent gender differences in the pharmacokinetics of NUEDEXTA.

#### *Race*

A population pharmacokinetic analysis of race with 109 subjects (21 Caucasian; 71 Hispanic; 18 Black) revealed no apparent racial differences in the pharmacokinetics of NUEDEXTA.

### *Renal Impairment*

In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg TWICE DAILY in 12 subjects with mild (CLCR 50-80 mL/min) or moderate (CLCR 30-50 mL/min) renal impairment (6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects showed little difference in quinidine or dextromethorphan pharmacokinetics compared to healthy subjects. Dose adjustment is, therefore, not required in mild or moderate renal impairment. NUEDEXTA has not been studied in patients with severe renal impairment.

### *Hepatic Impairment*

In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg TWICE DAILY in 12 subjects with mild or moderate hepatic impairment (as indicated by the Child-Pugh method; 6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects with moderate hepatic impairment showed similar dextromethorphan AUC and  $C_{max}$  and clearance compared to healthy subjects. Mild to moderate hepatic impairment had little effect on quinidine pharmacokinetics. Patients with moderate impairment showed an increased frequency of adverse events. Therefore, dosage adjustment is not required in patients with mild and moderate hepatic impairment, although additional monitoring for adverse reactions should be considered. Quinidine clearance is unaffected by hepatic cirrhosis, although there is an increased volume of distribution that leads to an increase in the elimination half-life. Neither dextromethorphan alone nor NUEDEXTA has been evaluated in patients with severe hepatic impairment.

## **12.4 Drug-Drug Interactions**

The potential for dextromethorphan and quinidine to inhibit or induce cytochrome P450 in vitro were evaluated in human microsomes. Dextromethorphan did not inhibit (<20% inhibition) any of the tested isoenzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 microM. Quinidine did not inhibit (<30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 microM. Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration ( $IC_{50}$ ) of less than 0.05 microM. Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 microM.

### Desipramine (CYP2D6 substrate)

Co-administration of dextromethorphan 30 mg/quinidine 30 mg with the tricyclic antidepressant desipramine, a CYP2D6 substrate, when desipramine was given at a dose of 25 mg once daily in 13 healthy volunteers resulted in an approximately 8-fold increase in steady state desipramine exposure ( $C_{min}$ ) compared to desipramine given alone. Therefore, concomitant administration of NUEDEXTA and drugs undergoing CYP2D6 metabolism should be evaluated for appropriate dose adjustment or alternative medication if the concomitant medication depends primarily on CYP2D6 metabolism and has a narrow therapeutic index, or if it relies on CYP2D6 for conversion to an active species [*see Warnings and Precautions (5.4)*].

### Paroxetine (CYP2D6 inhibitor and substrate)

Co-administration of the selective serotonin reuptake inhibitor paroxetine and a higher combination dose of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) was studied in 27 healthy volunteers. Group 1 (N = 14) received paroxetine 20 mg once daily for 12 days followed by the addition of dextromethorphan 30 mg/quinidine 30 mg twice daily for 8 days. Group 2 (N = 13) received dextromethorphan 30 mg/quinidine 30 mg twice daily for 8 days followed by the addition of paroxetine 20 mg once daily for 12 days. Dextromethorphan exposure ( $AUC_{0-12}$ ) and  $C_{max}$  increased by 1.5 fold and 1.4 fold, respectively, and quinidine exposure ( $AUC_{0-12}$ ) and  $C_{max}$  increased by 1.4 fold and 1.3 fold, respectively, and dextromethorphan exposure ( $AUC_{0-12}$ ) and  $C_{max}$  decreased by 14% and 18%, respectively, and

paroxetine exposure ( $AUC_{0-24}$ ) and  $C_{max}$  increased by 2.3 fold and 2.0 fold, respectively, when paroxetine was added to the combination dose of dextromethorphan/quinidine at steady state (Group 2).

When the combination dose of dextromethorphan/quinidine was added to paroxetine at steady state (Group 1), paroxetine exposure ( $AUC_{0-24}$ ) and  $C_{max}$  increased by 1.7 fold and 1.5 fold, respectively, while dextromethorphan and quinidine exposure did not change significantly and dextromethorphan exposure ( $AUC_{0-12}$ ) and  $C_{max}$  decreased by 34% and 33%, respectively.

Based on these results, when NUEDEXTA is prescribed with drugs such as paroxetine that inhibit or are extensively metabolized by CYP2D6, consideration should be given to initiating treatment with a lower dose. The dose of paroxetine can then be adjusted based on clinical response; however, dosage above 35 mg/day is not recommended [see *Warnings and Precautions (5.4)*].

#### NMDA receptor antagonists (memantine)

A drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) and memantine 20 mg/day to investigate the pharmacokinetic and pharmacodynamic interactions in 52 healthy subjects. Both dextromethorphan and memantine are antagonists of the *N*-methyl-D-aspartate (NMDA) receptor, which could theoretically result in an additive effect at NMDA receptors and potentially an increased incidence of adverse events. There was no significant difference in the plasma concentrations of dextromethorphan and dextromethorphan before and after the administration of memantine. Plasma concentrations of quinidine increased 20-30% when memantine was added to dextromethorphan 30mg/quinidine 30mg.

### **12.5 Pharmacogenomics**

The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-10% of Caucasians and 3-8% of African Americans generally lack the capacity to metabolize CYP2D6 substrates and are classified as PMs. The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA [see *Warnings and Precautions (5.4),(5.8)*, and *Clinical Pharmacology (12.3)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

In a 26-week carcinogenicity study in the Tg.rasH2 transgenic mouse, dextromethorphan and quinidine, alone and in combination, at oral doses up to 100/100 mg/kg/day did not show any evidence of carcinogenic potential.

In a two-year carcinogenicity study in rats, dextromethorphan/quinidine were administered at oral doses of 0/0, 5/100, 20/100, 50/100, 50/0, 0/100 mg/kg/day. No biologically significant tumor findings were observed. The highest dose tested (50/100 mg/kg/day) is approximately 12/50 times the recommended human dose (RHD) of 40/20 mg/day on a  $mg/m^2$  basis.

#### Mutagenesis

Dextromethorphan/quinidine was negative in an *in vitro* chromosomal aberration assay in human lymphocytes.

Dextromethorphan was negative in *in vitro* (bacterial reverse mutation, chromosomal aberration in human lymphocytes) and *in vivo* (mouse micronucleus) assays.

Quinidine was negative in an *in vitro* bacterial reverse mutation assay and in an *in vivo* mouse micronucleus assay. Quinidine induced chromosomal aberrations in an *in vitro* chromosomal aberration assay in the presence of metabolic activation.

#### Impairment of fertility

When dextromethorphan/quinidine was administered orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested, which is approximately 12/50 times the RHD on a mg/m<sup>2</sup> basis.

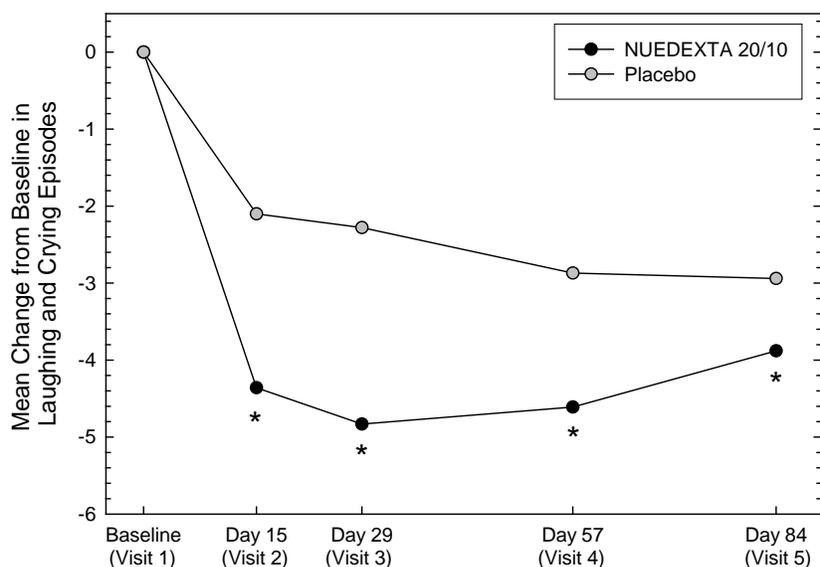
## **14 CLINICAL STUDIES**

The efficacy of NUEDEXTA was demonstrated in one trial in patients with pseudobulbar affect (PBA). These patients had underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Other trials at higher doses (dextromethorphan 30 mg/quinidine 30 mg) provided supportive evidence.

In the NUEDEXTA trial, patients with PBA were randomized to receive NUEDEXTA dextromethorphan 20 mg/quinidine 10 mg, (N=107), dextromethorphan 30 mg/quinidine 10 mg (N=110), or placebo (N=109) for 12 weeks.

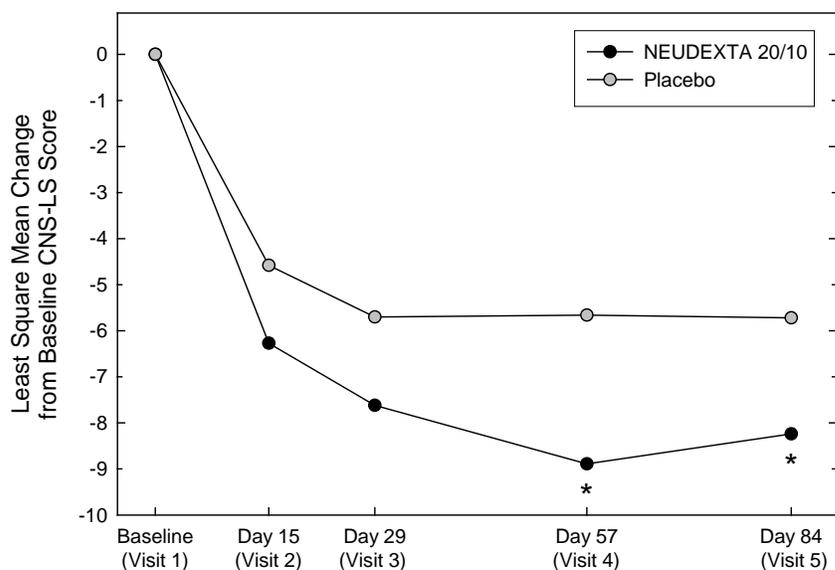
The primary outcome measure, laughing and crying episodes ([Figure 1](#)), was statistically significantly lower in each dextromethorphan/quinidine arm compared to placebo, based on an analysis of the sums of the episode counts over the double-blind phase. The secondary endpoint was the Center for Neurologic Studies Lability Scale (CNS-LS), a seven-item self-report questionnaire with 3 items assessing crying and 4 assessing laughter. CNS-LS was analyzed based on the difference between the mean scores on day 84 and baseline, and was also statistically significantly lower in each dextromethorphan/quinidine arm compared to placebo ([Figure 2](#)). There were no clinically important differences between NUEDEXTA and the dextromethorphan 30 mg/quinidine 10 mg arm.

### **Figure 1: Mean PBA Episode Rates by Visit**



\* Statistically significant at  $p < 0.05$

**Figure 2: Least Square Mean CNS-LS Scores by Visit**



\* Statistically significant at  $p < 0.05$

Two additional studies conducted using a higher dose combination of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) provided supportive evidence of NUEDEXTA efficacy. The first was a 4 week study in PBA patients with underlying ALS, and the second was a 12 week study in patients with underlying MS. In both studies, the primary outcome measure, CNS-LS, and the secondary outcome measure, laughing and crying episodes, were statistically significantly decreased by the dextromethorphan/quinidine combination.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

NUEDEXTA is supplied as brick red gelatin capsules imprinted with “DMQ / 20-10”. NUEDEXTA is supplied in the following package configuration:

Package Configuration	Capsule Strength (mg)	NDC Code
Bottles of 60 (30 day supply)	dextromethorphan 20 mg/ quinidine 10 mg	64597-301-60

### Storage

Store NUEDEXTA capsules at controlled room temperature, 25°C (77°F); excursions permitted to 15° - 30 °C (59° - 86°F) [See USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

### Hypersensitivity

Patients should be advised a hypersensitivity reaction to NUEDEXTA could occur. Patients should be instructed to seek medical attention immediately if they experience symptoms indicative of hypersensitivity after taking NUEDEXTA [see *Contraindications (4.2)*, *Warnings and Precautions (5.1)*].

### Cardiac effects

Patients should be advised to consult their healthcare provider immediately if they feel faint or lose consciousness. Patients should be counseled to inform their healthcare provider if they have any personal or family history of QTc prolongation [see *Contraindications (4.4)*, *Warnings and Precautions (5.3)* *Drug Interactions (7)*].

### Dizziness

Patients should be advised that NUEDEXTA may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls [see *Warnings and Precautions (5.5)*, *Adverse Reactions (6.1)*].

### Drug Interactions

Inform patients that NUEDEXTA increases the risk of adverse drug interactions, Instruct patients to inform their healthcare provider about all the medications that they are taking before taking NUEDEXTA. Before taking any new medications, patients should tell their healthcare provider that they are taking NUEDEXTA [see *Drug Interactions (7)*].

### Dosing Instructions

Instruct patients to take NUEDEXTA exactly as prescribed. Instruct patients not to take more than 2 capsules in a 24-hour period and to make sure that there is an approximate 12-hour interval between doses, and not to take a double dose after they miss a dose [see *Dosage and Administration (2.1)*].

### General

Patients should not share or give NUEDEXTA to others, even if they have the same symptoms, because it may harm them.

Advise patients to contact their healthcare provider if their PBA symptoms persist or worsen.

Advise patients to keep this and all medications out of reach of children and pets.

Marketed by:  
Avanir Pharmaceuticals, Inc.  
Aliso Viejo, CA 92656  
1-949-389-6700  
Revised January 2015

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21879S005**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	Prior Approval Labeling Supplement
Application Number(s)	N 21879 (Supplement S-005)
Priority or Standard	Standard
Submit Date	August 1, 2014
Received Date	August 1, 2014
PDUFA Goal Date	February 1, 2015
Reviewer Name	Devanand Jillapalli, MD
Review Completion Date	December 17, 2014
Established Name	Dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)
Trade Name	Nuedexta
Therapeutic Class	Uncompetitive NMDA receptor antagonist and sigma-1 agonist
Applicant	Avanir Pharmaceuticals
Formulation(s)	Capsule
Dosing Regimen	DM 20 mg/Q 10 mg, 1 capsule every 12 hours
Indication(s)	Treatment of pseudobulbar affect
Intended Population(s)	Adult patients with pseudobulbar affect

## **1 Recommendations/Risk Benefit Assessment**

### **Recommendation on Regulatory Action**

I recommend approval of the Prior Approval Supplement (S-005) which seeks to modify the language in the Indications and Usage section in order to clearly communicate the approved use of Nuedexta and the condition it affects. My recommendations for change in language in the Indications and Usage section are noted as track changes to the last approved label, the affected sections of which are reproduced in Section 9.2 of this review.

### **Risk Benefit Assessment**

The proposed labeling changes do not alter the risk-benefit profile of Nuedexta.

## **2 Introduction and Regulatory Background**

Nuedexta was approved on 10/29/2010 for the symptomatic treatment of pseudobulbar affect (PBA) in patients with neurological disease or injury. PBA occurs secondary to a variety of otherwise unrelated neurological conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state.

Nuedexta is a fixed combination of dextromethorphan hydrobromide (DM) 20 mg and quinidine sulfate (Q) 10 mg. DM is the pharmacologically active ingredient of Nuedexta that acts on the central nervous system, and is rapidly metabolized by CYP2D6-dependent oxidation. Q is a specific inhibitor of CYP2D6 and is used in Nuedexta to increase the systemic bioavailability of DM.

Three controlled efficacy trials of PBA subjects supported approval of Nuedexta: Study 102, Study 106 and the double-blind phase of Study 123. Studies 102 and 106 were submitted in support of the original New Drug Application (1/27/06); a higher dose of Q (DM 30 mg/Q 30 mg) was used in both of these studies. An Approvable Letter was issued on 10/30/06. In response to the Division of Neurology Product's (hereafter, referred to as the Division) suggestion in the Approvable Letter that a lower dose of Q be evaluated, the sponsor conducted Study 123 using a lower dose of Q (DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg). After reviewing the sponsor's

subsequent submission (4/30/10) addressing the deficiencies outlined in the Approvable Letter, the Division approved Nuedexta on 10/29/10.

The above controlled studies that supported approval of Nuedexta were performed in patients with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). At the time of approval of Nuedexta, after considering that ALS and MS are significantly and sufficiently different from each other in pathology and anatomic location of lesions, the Division concluded that effectiveness can reasonably be extrapolated to PBA that occurs in other neurologic conditions not studied in controlled trials.

Although the Division granted a global claim for PBA at approval, there were concerns about behavioral changes seen in patients with Alzheimer's disease (AD) that may mimic PBA, and whether PBA actually occurs in patients with AD remained unclear. Since the Sponsor believed that PBA does occur in AD, the Division expected that the sponsor would promote Nuedexta in patients with AD. Therefore, labeling was written to make it clear that PBA is a distinct syndrome, and that Nuedexta has not been shown to be safe and effective for any other behavioral abnormalities that might occur in the setting of other neurologic diseases.

Prior Approval supplemental application (S-003) which provided for extending the expiry date for the drug product from 30 months to 36 months was approved on 1/26/12. Prior Approval supplemental application (S-002), submitted on 5/26/11, was for additional new packaging configuration for Nuedexta capsules that consist of 13 count blister sample pack. On 4/26/11, a Prior Approval supplemental application (S-001) was submitted which provided for extending the expiry date for the drug product from 24 months to 30 months.

Since approval, the sponsor states that postmarketing experience with physicians, healthcare plans, and drug compendia indicate that there is frequent confusion about the product indication as being restricted to treat PBA secondary only to ALS or MS. On 5/21/13, the sponsor requested a Type B Meeting to discuss a proposed change to the indication language for Nuedexta to increase clarity of the approved indication. The Division responded that a meeting was not necessary, and directed the sponsor to submit the proposed labeling changes as a Prior Approval Supplement. (b) (4)

(b) (4) The Division communicated the need for user fee since it was not clear if the application was seeking to clarify the indication or broaden it. In response, the sponsor requested another meeting to discuss their intention to seek only clarification of the indication language. A Telecon between the Division and the sponsor was subsequently held on 7/29/14 to discuss clarification of the Nuedexta indication language. During this call, the Division agreed to clarify the Nuedexta indication language to avoid the misinterpretation that Nuedexta is approved for use in PBA patients with ALS or MS only. (b) (4)

(b) (4) filed this Prior Approval Labeling Supplement (S-005) application without new clinical data (subject of this review).

In this supplement (S-005), the Sponsor states that "...the wording used to define the scope of the approved indication has generated substantial confusion and misunderstanding in routine medical practice. As a consequence, a large number of patients with PBA secondary to "non-

ALS/MS conditions” who could be prescribed Nuedexta within the FDA approved indication are simply not offered this medication or are denied access by health plans. Unfortunately, the misinterpretation of the Nuedexta indication continues despite significant efforts made by Avanir (Sponsor) to educate health care providers on the full prescribing information.”

In this labeling supplement (S-005), the sponsor proposes a modification to the product indication statement of the Nuedexta labeling “to reduce misinterpretation of the approved indication, and more clearly communicate FDA’s determination that Nuedexta can be considered effective and is approved for use in all settings in which PBA occurs.” The Sponsor also notes “Importantly, the proposed changes will continue to provide clear information on the appropriate use of Nuedexta, also distinguishing PBA from other forms of emotional lability for which the drug has not been studied.”

Reviewer’s note on deletion of several sections of the NDA Review Template:

Several sections of the NDA Review Template are not relevant for the review of this Prior Approval Labeling Supplement S-005. The Manual of Policies and Procedures (MAPP) 6010.3 Rev.1 dated 12/10/10, Center for Drug Evaluation and Research, states that although the standardized structure of the NDA Review Template enables subsequent reviewers and other readers to readily locate specific information, the template can be adjusted and certain subsections omitted so that the review is not interrupted with multiple sections labeled “not applicable because...”. Since there are no clinical data to review, and consistent with the above-noted MAPP, I deleted Sections 3 to 9.1 from the Review Template. The main body of the review of this labeling supplement is located in Section 9.2 of this review.

## 9 Appendices

### 9.2 Labeling Review and Recommendations

As stated above, there are no clinical data in this application for review. The labeling changes that the sponsor proposes are to move existing language from Section 1 to Section 5.9, modify the description of PBA, and add new language in Section 14. The following is a review of the labeling changes proposed by the sponsor, sponsor's rationale for the proposed changes, followed by my conclusions and recommendations.

**Labeling changes proposed by the sponsor**

The sponsor proposes to add the text in red font and move portions of the deleted text from Section 1 Indications and Usage to (b) (4) Warnings and Precautions, as follows:

**1 INDICATIONS AND USAGE**  
NUEDEXTA is indicated for the

(b) (4)

(b) (4)

Additionally, the sponsor proposes to add new text (in red font) to Section 14 Clinical Studies, as follows:

**14 CLINICAL STUDIES**

The efficacy of NUEDEXTA was demonstrated in one trial in PBA patients with (b) (4) underlying (b) (4) amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Other trials at higher doses (dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg) provided supportive evidence. (b) (4)

(b) (4)

Sponsor's rationale for the above changes: The sponsor cites three label comprehension studies of product label, documentation of denials of prescription coverage from managed care patients, data from health plan formularies and from independent drug compendia, and concludes that providers and payers continue to believe that Nuedexta is restricted to use in patients with PBA secondary to only ALS or MS.

Further, citing the following two specific sources, the sponsor concludes that the language in these two sources implies that AD itself is a form of emotional lability, and therefore Nuedexta is not indicated for patients with AD even if they have PBA.

- The Special Populations section of Nuedexta monograph of Lexi-Comp (a clinical resource utilized by clinicians in making treatment-level decisions) reads: “Dementia:

Has not shown to be safe or effective in other types of commonly occurring emotional labilities (e.g., Alzheimer’s disease and other dementias).”

- The Nuedexta monograph published by the compendium Drugdex states:  
“Dextromethorphan hydrobromide/quinidine sulfate is indicated for the treatment of pseudobulbar affect. Clinical studies to support effectiveness were conducted in patients with underlying amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Safety and effectiveness in other types of emotional lability (e.g., Alzheimer disease, other dementias) have not been established”.

Reviewer’s conclusion and recommendation:

I agree with the sponsor that the language in the indication section of Nuedexta should be clarified to clearly state that Nuedexta is indicated for the treatment of PBA occurring in patients with underlying neurological disease or injury, consistent with the Division’s intent at approval to grant a broad claim for PBA regardless of the underlying neurological condition. In this regard, I agree that the current language in the indication which describes the patient population evaluated in clinical studies supporting approval has the potential for prescribing physicians and other stakeholders to misinterpret the indication as limiting Nuedexta to treat PBA secondary only to ALS and MS. Therefore, I recommend the removal of the following sentence from the indication: “Studies to support the effectiveness of NUEDEXTA were performed in patients with underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS).”

Especially when a broad claim is granted, it is important to accurately describe the condition for which the claim has been granted in order to appropriately distinguish it from the other features unique to the given underlying neurological condition, and to point out limitation(s) of use when such distinction may be potentially difficult. The sponsor proposes to move the description of PBA and limitations of use from Section 1 Indications and Usage to Section (b) (4) Warnings and Precautions. Importantly, the physical separation of description of the PBA and limitations of use from the proposed indication makes it difficult to communicate the approved use of Nuedexta and the condition it affects in an accurate and informative manner. The sponsor states that a reason for the proposed labeling changes is the language in two sources (cited above) which imply that AD itself is a form of emotional lability. However, progressive dementia, not emotional lability, is the core manifestation of AD. Emotional lability may be present in a proportion of patients but to consider it as the defining feature of AD is erroneous. Labeling change is not the appropriate method to correct the erroneous language in the cited sources. Communicating that PBA is distinct from other emotional labilities that occur in neurological diseases in effect defines the approved indication and is not necessarily a limitation of use. For these reasons, I recommend the retention of currently approved location (in Indications and Usage section) and the language describing PBA, and modification of language that states that PBA is distinct from other emotional labilities.

The sponsor’s proposal to add the two phrases (b) (4)” and (b) (4)” to describe the study populations (ALS and MS) in section 14 Clinical Studies is not informative. In

addition, the proposal to add the following sentence (b) (4)

(b) (4) is an indication statement that is implied in the current language (after removal of the sentence describing the patient population evaluated in clinical studies supporting approval), and therefore, is redundant in content and inappropriate in location (Clinical Studies).

My labeling recommendations are reflected as track changes to the last approved label, and the affected sections of which are reproduced below.

## 1 INDICATIONS AND USAGE

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.

(b) (4)

## 14 CLINICAL STUDIES

The efficacy of NUEDEXTA was demonstrated in one trial in (b) (4) patients with pseudobulbar affect (PBA). These patients had underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Other trials at higher doses (dextromethorphan 30 mg/quinidine 30 mg) provided supportive evidence.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEVANAND JILLAPALLI  
12/18/2014

RONALD H FARKAS  
12/22/2014